Public Assessment Report

Decentralised Procedure

DCPAR

Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.5 mg/mL, 0.2 mg/mL Solution for Injection or Concentrate for Solution for Infusion

UK/H/2339/01-03/DC
UK/H/2340/01/DC

UK licence no: PL 00289/1257
PL 00289/1264
PL 00289/1265
PL 00289/1140

Applicant: TEVA UK Limited
LAY SUMMARY

The MHRA granted TEVA UK Limited Marketing Authorisations (licences) for the medicinal products Octreotide 0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion on 23 December 2011 and Octreotide 0.2 mg/mL Solution for Injection or Concentrate for Solution for Infusion on 22 December 2011. These are prescription-only medicines.

Octreotide is a synthetic form of a hormone called somatostatin which occurs naturally in the body. It helps stop the release of some hormones, including growth hormone, in the body.

Octreotide is used to treat acromegaly; a condition where the body produces too much growth hormone. The level of growth hormone controls the growth of tissues, organs and bones. Too much growth hormone means the size of bones and tissues, especially in the hands and feet are larger than normal.

Octreotide is used to treat people with acromegaly: when other types of treatment (surgery or radiotherapy) are not suitable or have not worked; after radiotherapy, to cover the interim period until the radiotherapy becomes effective and before surgery on the pituitary gland.

Octreotide is also used to relieve stomach or bowel symptoms associated with certain tumours known as ‘gastroenteropancreatic’ tumours (rare tumours of the stomach, bowels or pancreas).

Octreotide is also used to prevent complications following pancreatic surgery.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of using Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion outweigh the risks and Marketing Authorisations were granted.
# TABLE OF CONTENTS

| Module 1: Information about initial procedure | Page 4 |
| Module 2: Summary of Product Characteristics | Page 5 |
| Module 3: Patient Information Leaflets | Page 14 |
| Module 4: Labelling | Page 19 |
| Module 5: Scientific Discussion | Page 25 |
| 1 Introduction | Page 25 |
| 2 Quality aspects | Page 29 |
| 3 Non-clinical aspects | Page 32 |
| 4 Clinical aspects | Page 32 |
| 5 Overall conclusions | Page 35 |
| Module 6: Steps taken after initial procedure | Page 36 |
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Octreotide 0.05, 0.1, 0.2, 0.5 mg/ml Solution for Injection or Concentrate for Solution for Infusion.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Octreotide Acetate</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Solution for Injection or Concentrate for Solution for Infusion</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>0.05, 0.1, 0.2, 0.5 mg/ml</td>
</tr>
</tbody>
</table>
| **MA Holder** | TEVA UK Limited  
Brampton Road,  
Hampden Park,  
Eastbourne,  
East Sussex BN22 9AG  
UNITED KINGDOM |
| **Reference Member State (RMS)** | UK |
| **CMS** | Octreotide 0.05 mg/mL Solution for Injection or Concentrate for Solution for Infusion  
PL 00289/1257;UK/H/2339/01/DC: Belgium, Germany, Italy, Luxembourg, the Netherlands, Portugal and Spain,  
Octreotide 0.1 mg/mL Solution for Injection or Concentrate for Solution for Infusion  
PL 00289/1264; UK/H/2339/02/DC: Belgium, Germany, Hungary, Italy, Luxembourg, the Netherlands, Portugal and Spain,  
Octreotide 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion  
PL 00289/1265;UK/H/2339/03/DC: Belgium, Germany, Italy, Luxembourg, the Netherlands and Portugal  
Octreotide 0.2 mg/mL Solution for Injection or Concentrate for Solution for Infusion  
PL 00289/1140;UK/H/2340/01/DC: Germany and the Netherlands |
| **Procedure Number** | UK/H/2339/01-03/DC  
UK/H/2340/01/DC |
| **End of Procedure** | 4 November 2011 |
Module 2

Summary of Product Characteristics

The UK Summary of Product Characteristics (SmPCs) for Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion (PL 00289/1257, PL 00289/1264, PL 00289/1140 and PL 00289/1265) are as follows: Differences between the SmPCs are highlighted in yellow.

1 NAME OF THE MEDICINAL PRODUCT
Octreotide 0.05mg/ml Solution for Injection or Concentrate for Solution for Infusion
Octreotide 0.1mg/ml Solution for Injection or Concentrate for Solution for Infusion
Octreotide 0.2mg/ml Solution for Injection or Concentrate for Solution for Infusion
Octreotide 0.5mg/ml Solution for Injection or Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of Octreotide solution for injection or concentrate for solution for infusion contains 0.05mg, 0.1mg, 0.2mg, 0.5mg of octreotide (as octreotide acetate) respectively.

Octreotide solution for injection or concentrate for solution for infusion contains less than 1 mmol (23mg) sodium per dose, i.e essentially “sodium-free”.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM
Solution for injection (s.c) or concentrate for solution for infusion.

pH: 3.7 to 4.7
Osmolality:
- 315 to 350 mOsmol/kg (For 0.05 mg/mL, 0.1 mg/mL and 0.5mg/mL strengths)
- 340 to 410 mOsmol/kg (For 0.2 mg/mL strength)

The solution is clear and colourless.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications

GEP tumours:
For the relief of symptoms associated with functional gastroenteropancreatic endocrine tumours including:
- Carcinoid tumours with features of carcinoid syndrome
- VIPomas
- Glucagonomas

Octreotide is not an antitumour therapy and is not curative in these patients.

Acromegaly:
For symptomatic control and reduction of growth hormone and somatomedin c plasma levels in patients with acromegaly:
- In short term treatment, prior to pituitary surgery, or
- In long term treatment in those who are inadequately controlled by pituitary surgery, radiotherapy, or in the interim period until radiotherapy becomes effective.

Octreotide is indicated for acromegalic patients for whom surgery is inappropriate.

Evidence from short term studies demonstrate that tumour size is reduced in some patients (prior to surgery) further tumour shrinkage however cannot be expected as a feature of continued long term treatment.
Prevention of complications following pancreatic surgery.

4.2 Posology and method of administration

Route of administration

Subcutaneous or intravenous use.

To reduce local discomfort, let the solution reach room temperature before injection. Avoid multiple injections at short intervals at the same time.

GEP tumours

Initially 0.05 mg once or twice daily by s.c. injection. Depending on response, dosage can be gradually increased to 0.2 mg three times daily. Under exceptional circumstances, higher doses may be required. Maintenance doses are variable.

The recommended route of administration is subcutaneous, however, in instances where a rapid response is required, e.g. carcinoid crises, the initial recommended dose of Octreotide may be administered by the intravenous route, diluted and given as a bolus, whilst monitoring the cardiac rhythm.

In carcinoid tumours, if there is no beneficial effect within a week, continued therapy is not recommended.

Acromegaly

0.1 – 0.2 mg three times daily by s.c. injection. Dosage adjustment should be based on monthly assessment of GH and IGF-1 levels (target: GH less than 2.5 ng/ml, 5mU/l; IGF-1 within normal range) and clinical symptoms, and on tolerability.

For patients on a stable dose of Octreotide, assessment of GH should be made every 12 months. Six-monthly monitoring may be necessary in those patients whose clinical and biochemical control is adequate.

If no relevant reduction of growth hormone levels and no improvement of clinical symptoms have been achieved within three months of starting treatment, therapy should be discontinued.

For the prevention of complications following pancreatic surgery:

0.1 mg three times daily by subcutaneous injection for 7 consecutive days, starting on the day of operation at least one hour before laparotomy.

Use in patients with impaired renal function:

Impaired renal function did not affect the total exposure (AUC; area under the curve) to octreotide when administered subcutaneously, and therefore no dose adjustment of Octreotide is necessary.

Use in patients with impaired liver function:

In patients with liver cirrhosis, the half-life of the drug may be increased, necessitating adjustment of the maintenance dosage.

Use in the elderly:

In elderly patients treated with Octreotide, there was no evidence for reduced tolerability or altered dosage requirements.

Paediatric population:

Experience with the use of Octreotide in children is very limited.
4.3 Contraindications
Known hypersensitivity to octreotide or to any of the excipients.

4.4 Special warnings and precautions for use

General
As growth hormone secreting pituitary tumours may sometimes expand, causing serious complications (e.g. visual field defects), it is essential that all patients be carefully monitored. If evidence of tumour expansion appears, alternative procedures may be advisable.

The therapeutic benefits of a reduction in growth hormone (GH) levels and normalisation of insulin-like growth factor 1 (IGF-1) concentration in female acromegalic patients could potentially restore fertility. Female patients of child bearing potential should be advised to use adequate contraception if necessary during treatment with octreotide (see also section 4.6).

Thyroid function (TSH and thyroid hormone levels) should be monitored in patients receiving long-term Octreotide therapy.

Cardiovascular related events
Uncommon cases of bradycardia have been reported. Dose adjustments of drugs such as beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may be necessary.

GEP endocrine tumours
Sudden escape of gastroenteropancreatic endocrine tumours from symptomatic control by Octreotide may occur infrequently, with rapid recurrence of severe symptoms.

Glucose metabolism
Because of its inhibitory action on growth hormone, glucagon and insulin release, octreotide may affect glucose regulation. Postprandial glucose tolerance may be impaired and, in some instances, the state of persistent hyperglycaemia may be induced as a result of chronic administration. Hypoglycaemia has also been observed.

Octreotide may increase the depth and duration of hypoglycaemia in patients with insulinoma. This is because it is relatively more potent in inhibiting growth hormone and glucagon secretion than in inhibiting insulin and because its duration of insulin inhibition is shorter. If Octreotide is given to a patient with insulinoma, close monitoring is necessary on introduction of therapy and at each change of dosage. Marked fluctuations of blood glucose may be reduced by more frequent administration of Octreotide.

Octreotide may reduce insulin or oral hypoglycaemic requirements in patients with type I diabetes mellitus. In non-diabetics and type II diabetics with particularly intact insulin reserves, Octreotide administration can result in prandial increases in glycaemia. It is therefore recommended to monitor glucose tolerance and antidiabetic treatment.

Gallbladder and related events
Octreotide exerts an inhibiting effect on gallbladder motility, bile acid secretion and bile flow and there is an acknowledged association with the development of gallstones. The incidence of gallstone formation with Octreotide treatment is estimated to be between 15–30%. Ultrasonic examination of the gallbladder, before and at about 6 to 12 month intervals during Octreotide therapy is therefore recommended. If gallstones do occur, they are usually asymptomatic; symptomatic stones should be treated in the normal manner with due attention to abrupt withdrawal of the drug.
In patients with cirrhosis, dosage adjustment may be necessary (see Section 4.2).

Local Site Reactions
In a 52-week toxicity study in rats, predominantly in males, sarcomas were noted at the s.c. injection site only at the highest dose (about 40 times the maximum human dose). No hyperplastic or neoplastic lesions occurred at the s.c. injection site in a 52-week dog toxicity study. There have been no reports of tumour formation at the injection sites in patients treated with Octreotide for up to 15 years. All the information available at present indicates that the
findings in rats are species specific and have no significance for the use of the drug in humans.

Nutrition
Octreotide may alter absorption of dietary fats in some patients.
Depressed vitamin B₁₂ levels and abnormal Schilling's tests have been observed in some patients receiving octreotide therapy. Monitoring of vitamin B₁₂ levels is recommended during therapy with Octreotide in patients who have a history of vitamin B₁₂ deprivation.

4.5 Interaction with other medicinal products and other forms of interaction
Octreotide has been reported to reduce the intestinal absorption of ciclosporin and to delay that of cimetidine.

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine.

Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolised by CYP3A4 and which have a low therapeutic index should therefore be used with caution (e.g. carbamazepine, digoxin, terfenadine).

4.6 Fertility, pregnancy and lactation
Pregnancy
Octreotide should only be prescribed to pregnant women under compelling circumstances (see also section 4.4).

There are no adequate and well-controlled studies in pregnant women. In the post-marketing experience, data on a limited number of exposed pregnancies have been reported in patients with acromegaly, however, in half of the cases the pregnancy outcomes are unknown. Most women were exposed to octreotide during the first trimester of pregnancy at doses ranging from 100-300 micrograms/day of Octreotide s.c. or 20-30 mg/month of Octreotide LAR. In approximately two-thirds of the cases with known outcome, the women elected to continue octreotide therapy during their pregnancies. In most of the cases with known outcome, normal newborns were reported, but also several spontaneous abortions during the first trimester, and a few induced abortions.

There were no cases of congenital anomalies or malformations due to octreotide usage in the cases that reported pregnancy outcomes.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development apart from some transient retardation of physiological growth (see section 5.3).

Lactation
Patients should not breastfeed during Octreotide treatment. It is unknown whether octreotide is excreted in human breast milk. Animal studies have shown excretion of octreotide in breast milk.

4.7 Effects on ability to drive and use machines
No data exists on the effects of Octreotide on the ability to drive and use machines.

4.8 Undesirable effects
The most frequent adverse reactions reported during octreotide therapy include gastrointestinal disorders, nervous system disorders, hepatobiliary disorders, and metabolism and nutritional disorders.

The most commonly reported adverse reactions in clinical trials with octreotide administration were diarrhoea, abdominal pain, nausea, flatulence, headache, cholelithiasis, hyperglycaemia and constipation. Other commonly reported adverse reactions were dizziness,
Localised pain, biliary sludge, thyroid dysfunction (e.g. decreased thyroid stimulating hormone [TSH], decreased Total T4, and decreased Free T4), loose stools, impaired glucose tolerance, vomiting, asthenia and hypoglycaemia.

In rare instances, gastrointestinal side-effects may resemble acute intestinal obstruction with progressive abdominal distension, severe epigastric pain, abdominal tenderness and guarding. Pain or a sensation of stinging, tingling or burning at the site of s.c. injection, with redness and swelling, rarely lasting more than 15 minutes. Local discomfort may be reduced by allowing the solution to reach room temperature before injection.

Although measured faecal fat excretion may increase, there is no evidence to date that long-term treatment with octreotide has led to nutritional deficiency due to malabsorption. Occurrence of gastrointestinal side-effects may be reduced by avoiding meals around the time of octreotide administration, that is, by injecting between meals or on retiring to bed. In rare instances, acute pancreatitis has been reported; generally, this effect is seen within the first hours or days of octreotide treatment and resolves on withdrawal of the drug. In addition, cholelithiasis-induced pancreatitis has been reported for patients on long-term octreotide treatment.

There have been isolated cases of biliary colic following the abrupt withdrawal of the drug in acromegalic patients in whom biliary sludge or gallstones had developed. In both acromegalic and carcinoid syndrome patients ECG changes were observed such as QT prolongation, axis shifts, early repolarisation, low voltage, R/S transition, early R wave progression, and non-specific ST-T wave changes. The relationship of these events to octreotide acetate is not established because many of these patients have underlying cardiac diseases (see section 4.4). The following adverse drug reactions, listed in Table 1, have been accumulated from clinical studies with octreotide:

Adverse drug reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000); Not known (cannot be estimated from the available data) including isolated reports. Within each frequency grouping adverse reactions are ranked in order of decreasing seriousness.

**Table - Adverse drug reactions**

<table>
<thead>
<tr>
<th>Category</th>
<th>Exemplary Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine disorders</strong></td>
<td>Hypothyroidism, thyroid dysfunction (e.g., decreased TSH, decreased Total T4 and decreased Free T4)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td>Hyperglycaemia, impaired glucose tolerance, anorexia</td>
</tr>
<tr>
<td>Very common:</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders:</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders:</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Respiratory disorders:</td>
<td>Dyspnoea</td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders:</td>
<td>Diarrhoea, abdominal pain, nausea, constipation, flatulence</td>
</tr>
<tr>
<td>Very common:</td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td>Dyspepsia, vomiting, abdominal bloating, steatorrhoea, loose stools, discolouration of faeces</td>
</tr>
<tr>
<td>Nervous system disorders:</td>
<td>Headache</td>
</tr>
<tr>
<td>Very common:</td>
<td></td>
</tr>
<tr>
<td>Common:</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders:</td>
<td>Cholelithiasis</td>
</tr>
<tr>
<td>Very common:</td>
<td></td>
</tr>
</tbody>
</table>
### Common:
- Cholecystitis, biliary sludge, hyperbilirubinaemia

### Not known
- Acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice

### Skin and subcutaneous tissue disorder
- Common: Pruritus, rash, alopecia
- Not known: Urticaria

### General disorders and administration site
- Common: Injection site localised pain

### Investigations
- Common: Elevated transaminase levels
- Not known: Increased alkaline phosphatase levels, increased gamma glutamyl transferase levels

### Immune disorders
- Not known: Anaphylaxis, allergy/hypersensitivity reactions

### 4.9 Overdose
A limited number of accidental overdoses of Octreotide in adults and children have been reported. In adults, the doses ranged from 2400-6000 micrograms/day administered by continuous infusion (100-250 micrograms/hour) or subcutaneously (1500 micrograms t.i.d.). The adverse events reported were arrhythmia, hypotension, cardiac arrest, brain hypoxia, pancreatitis, hepatitis steatosis, diarrhoea, weakness, lethargy, weight loss, hepatomegaly and lactic acidosis.

In children, the doses ranged from 50-3000 micrograms/day administered by continuous infusion (2.1-500 micrograms/hour) or subcutaneously (50-100 micrograms). The only adverse event reported was mild hyperglycaemia.

No unexpected adverse events have been reported in cancer patients receiving Octreotide at doses of 3000-30,000 micrograms/day in divided doses subcutaneously. The management of overdosage is symptomatic.

### 5 PHARMACOLOGICAL PROPERTIES
#### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antigrowth hormones
ATC code: H01CB02.

Octreotide is a synthetic octapeptide derivative of naturally occurring somatostatin with similar pharmacological effects, but with a longer duration of action. It inhibits pathologically increased secretion of growth hormone and of peptides and serotonin produced within the gastroenteropancreatic endocrine (GEP) system.

In animals, octreotide is a more potent inhibitor of growth hormone, glucagon and insulin release than somatostatin with greater selectivity for growth hormone and glucagon suppression.

In normal healthy subjects octreotide, like somatostatin, has been shown to inhibit - release of growth hormone stimulated by arginine, exercise and insulin-induced hypoglycaemia;

- postprandial release of insulin, glucagon, gastrin other peptides of the gastroenteropancreatic system; arginine-stimulated release of insulin and glucagon and

- thyrotropin-releasing hormone (TRH) - stimulated release of thyroid stimulating hormone (TSH).
Unlike somatostatin, octreotide inhibits growth hormone preferentially over insulin and its administration is not followed by rebound hypersecretion of hormones (i.e. growth hormone in patients with acromegaly).

For patients undergoing pancreatic surgery, the peri and post-operative administration of Octreotide reduces the incidence of typical post-operative complications (e.g. pancreatic fistula, abscess and subsequent sepsis, post-operative acute pancreatitis).

In patients with acromegaly, Octreotide consistently lowers GH and normalises IGF-1 serum concentrations in the majority of patients. In most patients, Octreotide markedly reduces the clinical symptoms of the disease, such as headache, perspiration, paresthesia, fatigue, osteoarthralgia and carpal tunnel syndrome. In individual patients with GH-secreting pituitary adenoma, Octreotide was reported to lead to shrinkage of the tumour mass. For patients with functional tumours of the gastroenteropancreatic endocrine system, treatment with octreotide provides continuous control of symptoms related to the underlying disease. The effect of octreotide in different types of gastroenteropancreatic tumours are as follows:

Carcinoid tumours: Administration of octreotide may result in improvement of symptoms, particularly of flushing and diarrhoea. In many cases, this is accompanied by a falling plasma serotonin and reduced urinary excretion of 5-hydroxyindole acetic acid.

VIPomas: The biochemical characteristics of these tumours is overproduction of vasoactive intestinal peptide (VIP). In most cases, administration of octreotide results in alleviation of the severe secretory diarrhoea typical of the condition, with consequent improvement in quality of life. This is accompanied by an improvement in associated electrolyte abnormalities, e.g. hypokalaemia, enabling enteral and parenteral fluid and electrolyte supplementation to be withdrawn. Clinical improvement is usually accompanied by a reduction in plasma VIP levels, which may fall into the normal reference range.

Glucagonomas: Administration of octreotide results in most cases in substantial improvement of the necrolytic migratory rash which is characteristic of the condition. The effect of octreotide on the state of mild diabetes mellitus which frequently occurs is not marked and, in general, does not result in a reduction of requirements for insulin or oral hypoglycaemic agents. Octreotide produces improvement of diarrhoea, and hence weight gain, in those patients affected. Although administration of octreotide often leads to an immediate reduction in plasma glucagon levels, this decrease is generally not maintained over a prolonged period of administration, despite continued symptomatic improvement.

5.2 Pharmacokinetic properties

Absorption
After subcutaneous administration, Octreotide is rapidly and completely absorbed. The peak plasma concentration is reached within 30 minutes.

Distribution
The volume of distribution is 0.27 l/kg and the total body clearance 160 ml/min. Plasma protein binding is approximately 65%. The amount of octreotide bound to blood cells is negligible.

Elimination
The elimination half-life after subcutaneous administrations is 100 minutes. After intravenous injection the elimination is biphasic with half-lives of 10 and 90 minutes. About 32% is excreted unchanged in the urine.

5.3 Preclinical safety data

Preclinical data reveal no specific hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Studies in animals showed transient growth retardation of offspring, possibly consequent upon the specific endocrine profiles of the species tested, but there was no evidence of foetotoxic, teratogenic, or other reproduction effects.
6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Glacial acetic acid (for pH adjustment)
Sodium acetate trihydrate (for pH adjustment) (E262)
Mannitol (E421)
Water for injections
Phenol (For 0.2 mg/mL strength only)

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those
mentioned in section 6.6.

6.3 Shelf life
Unopened vials: 3 years for 0.05 mg/mL, 0.1 mg/mL, 0.5 mg/mL strengths
Unopened vials: (2 years for 0.2 mg/mL strength)

Shelf life after first opening: The product must be used immediately and any unused drug
product must be discarded. (For 0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL strengths only)

Shelf life after first opening: Opened vials may be stored for 2 weeks at room temperature for
day to day use. (For 0.2 mg/mL strength only)

Storage conditions after dilution: The chemical and physical stability of Octreotide solution
diluted in 9 mg/ml (0.9%) sodium chloride solution for infusion has been demonstrated for 24
hours when stored below 25°C. From a microbiological point of view, the product should be
used immediately, if not used immediately, storage times and conditions are the responsibility
of the user, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Unopened vial: Store in a refrigerator between 2-8°C, protected from light. Do not freeze.

For storage conditions of the diluted medicinal product, see section 6.3. (For 0.05 mg/mL,
0.1 mg/mL and 0.5 mg/mL strengths only)

For storage conditions of the opened vial and diluted medicinal product, see section 6.3. (For
0.2 mg/mL strength only)

6.5 Nature and contents of container
Octreotide solution for injection or concentrate for solution for infusion is filled into clear
glass vials closed with rubber stoppers and sealed with aluminium flip-off caps fitted with
plastic flip-off discs. The product is packaged in cardboard boxes.

Packs sizes of 1, 3, 5, 6, 10, 20 and 30 vials. (For Strengths 0.05 mg/mL, 0.1 mg/mL and
0.5 mg/mL strengths only).

Pack sizes 1, 5 and 10 vials (For 0.2 mg/mL strength only)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
For i.v. use Octreotide should be diluted with normal saline to a ratio of not less than 1 vol :
1 vol and not more than 1 vol : 9 vol. Dilution of Octreotide with glucose is not
recommended.

If Octreotide has been diluted, the prepared solution may be kept at room temperature but
should be administered within 24 hours of preparation.

Single use only. (For 0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL strengths only)

To prevent contamination, it is recommended to puncture the cap of the vial not more than 10
times. (For 0.2 mg/mL strength only)
Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
TEVA UK Limited
Brampton Road,
Hampden Park,
Eastbourne,
East Sussex BN22 9AG
UNITED KINGDOM

8 MARKETING AUTHORISATION NUMBER(S)
PL 00289/1257
PL 00289/1264
PL 00289/1140
PL 00289/1265

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/12/2011 (For 0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL strengths only)
22/12/2011

10 DATE OF REVISION OF THE TEXT
23/12/2011 (For 0.05 mg/mL, 0.1 mg/mL and 0.5 mg/mL strengths only)
22/12/2011
Module 3
Patient Information Leaflet

1. What Octreotide is and what it is used for

Octreotide is a synthetic form of a hormone called somatostatin which occurs naturally in the body. It helps stop the release of some hormones, including growth hormone, in the body.

Octreotide is used:
- To treat acromegaly
  Acromegaly is a condition where the body produces too much growth hormone. The level of growth hormone controls the growth of tissues, organs and bones. Too much hormone means the size of bones and tissues, especially in the hands and feet, is larger than normal. The symptoms of acromegaly include headache, excessive perspiration, numb hands and feet, tiredness and joint pain. In most cases, the overproduction of growth hormone is caused by an enlargement in the pituitary gland (a pituitary adenoma).
  Octreotide is used to treat people with acromegaly;
  - when other types of treatment for acromegaly (surgery or radiotherapy) are not suitable or have not worked;
  - after radiotherapy, to cover the interim period until the radiotherapy becomes fully effective;
  - before surgery on the pituitary gland.

Growth hormone secreting pituitary tumours may sometimes expand and cause problems. Tell your doctor if you experience any problems with your eyes or sight.

Tell your doctor if your stomach or bowel problems get worse.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines, including medicines obtained without a prescription:
- Insulin or other drugs for diabetes
- Ciclosporin (a drug used after a transplant)
- Cimetidine (a drug used to reduce stomach acid)
- Bromocriptine (a drug used in Parkinson’s disease or in acromegaly to suppress breast milk)
- Medicines to control blood pressure (beta-blockers or calcium channel blockers) or agents to control fluid and electrolyte balance (diuretics)
- Medicines metabolised by the liver for example carbamazepine (a drug used in psychiatric disorders, epilepsy, trigeminal neuralgia and neuropathy), digoxin (medicine for certain heart problems) and warfarin (a drug used to thin the blood) and terfenadine (to relieve allergic symptoms).

Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicines. You should not use Octreotide if you are pregnant unless you have been told by your doctor that it is absolutely necessary for you to do so. You should not breast-feed your infant whilst receiving treatment with octreotide, unless you have been told to do so.

Driving and using machines
Octreotide may make you feel dizzy. If this happens, do not drive or operate machinery. Remember that if you are unwell your ability to operate machinery may be affected.

Important information about some of the ingredients of Octreotide
Octreotide 0.05 mg/ml, 0.1 mg/ml and 0.5 mg/ml solution for injection or concentrate for solution for infusion contains less than 1 mmol sodium per dose, i.e. essentially “sodium-free”.

Other Special Warnings
- Tell your doctor if your stomach or bowel symptoms get worse
- Octreotide should only be used in pregnancy if clearly needed. Tell your doctor if you are pregnant or want to become pregnant
- Women of child bearing potential must use an
• To relieve stomach or bowel symptoms associated with certain tumours known as ‘gastroenteropancreatic’ tumours (rare tumours of the stomach, bowels or pancreas)
  Overproduction of specific hormones and other related natural substances can be caused by some rare conditions of the stomach, bowels or pancreas. This upsets the natural hormonal balance of the body, and results in a variety of symptoms, such as flushing, diarrhoea, low blood pressure, rash and weight loss. Treatment with Octreotide helps to control these symptoms.

• To prevent complications following pancreatic surgery
  Octreotide can be used in some patients when they have an operation on the pancreas. It may help reduce some of the problems which can occur in the abdomen after the operation, such as inflammation (swelling) and infection.

BEFORE OCTREOTIDE IS USED
You should NOT be given Octreotide
• if you are allergic (hypersensitive) to octreotide acetate or any of the other ingredients of Octreotide (see section 6)
• if you are breast-feeding.

Take special care with Octreotide
• if you are pregnant
• as octreotide may affect your blood sugar levels. You or your doctor should closely monitor your blood sugar levels
• if you have any thyroid problems, or have had a disease which may have affected your thyroid
• if you have any problems with your liver, or have had a disease which may have affected your liver
• if you have ever suffered from gallstones or other stomach problems
• if you have a history of Vitamin B12 deficiency. Your doctor may need to monitor your vitamin B12 levels during therapy with octreotide.

Your doctor may want to give you a check up from time to time while you are being treated with Octreotide.

The following information is intended for medical or healthcare professionals only:

Instructions for use, handling and disposal:
For single use only.

Octreotide is an injection and a concentrate for solution for infusion. This must be handled with caution. The dilution must be done under aseptic conditions, by trained staff and in a specific area. The contact of Octreotide with skin and membranes should be avoided. If the solution comes into contact with the skin, wash with water and soap. If the solution comes into contact with membranes, wash (irigate) the affected area with water.

To reduce local discomfort, let the solution reach room temperature before injecting. Avoid multiple injections at short intervals at the same time.

Storage:
Storage conditions:
Before opening: Store in a refrigerator 2-8°C, protected from light. Do not freeze.
After opening: The product must be used immediately and any unused drug-product must be discarded.

HOW TO USE OCTREOTIDE
Always use Octreotide exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure of anything.

Your medicine must be injected subcutaneously i.e. into the tissue under the skin. Your doctor or nurse will show you how to do this. If you are unsure, go back and ask for advice. You must use a clean, sterile syringe and needle every time.

The upper arms, thighs and stomach are good areas for subcutaneous injection. Choose a different place each time so that you don’t irritate a particular area. Keep changing the injection site. Don’t inject into the same place too frequently.

To avoid side effects like stomach ache, wind, diarrhoea and constipation do not inject at mealtimes. Inject between meals or before going to bed.

In rare cases Octreotide will have to be injected intravenously (into a vein). If this is necessary the doctor or nurse will do it and monitor you closely. You must NOT inject Octreotide into your veins yourself.

The usual dosages are given below; however your doctor will decide what dosage to give to you, as this depends on the nature of your treatment, your age and your medical condition:

For the treatment of acromegaly
• The usual dose is 0.1 to 0.2 mg three times a day by subcutaneous injection. Depending on how you respond, your doctor will adjust the dose until they find the right dose.

To relieve symptoms caused by over-production of some hormones
• Your doctor will usually start your treatment with 0.05 mg once or twice daily by subcutaneous injection. Depending on how you respond, your doctor may gradually increase the dose until they find your ideal dose.
To prevent complications following pancreatic surgery
- 0.1 mg three times a day for seven days starting on the day of the operation.

People with liver or kidney problems may be given a smaller dose.

There is very little experience of using octreotide in children

**If you receive more Octreotide than you should**
If you are concerned that you may have been given too much Octreotide, tell your doctor or nurse immediately.

**If you miss a dose of Octreotide**
As you will be given this medicine under close supervision, it is very unlikely that you will miss a dose. If you think that you have missed a dose of treatment, tell a doctor or nurse at once.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

**4** POSSIBLE SIDE EFFECTS

Like all medicines, Octreotide can cause side effects, although not everybody gets them.

Most people who are prescribed Octreotide benefit from taking it, but a few people can be upset by it. If you are receiving this medicine on a long term basis then you will go to hospital from time to time to have regular check-ups.

There is no need to worry if you suffer from any of the following common reactions at the site of injection:
- Pain, tingling, burning, redness and swelling.
  These rarely last for more than 15 minutes and will be less if you let your medicine reach room temperature before injecting.

Some side effects can be serious. Stop taking Octreotide and tell your doctor straight away if you notice that:
- Your face becomes flushed or swollen or you develop spots or a rash.
- Your chest feels tight, you become short of breath or wheezy.
- You feel faint, possibly as a result of a fall in blood pressure.

These might be a result of an allergic reaction.

If you develop any of the following see your doctor immediately:
- Prolonged/troublesome bloating of the stomach with pain
- Nausea/vomiting associated with drowsiness
- Feeling restless or giddy
- Yellowing of the skin or whites of your eyes
- Acute pancreatitis (sudden, severe, burning pains in the stomach). This may happen within the first few hours or days of treatment and resolves itself upon drug withdrawal.

Uncommon:
- Dehydration
- Fast heart beat.

**Frequency not known:**
- Anaphylaxis (a type of allergic reaction which causes difficulty in breathing or dizziness), allergy/hypersensitivity reactions
- Itchy rash
- Inflammation of the pancreas
- Liver inflammation (hepatitis); symptoms may include yellowing of the skin and eyes (jaundice), nausea, vomiting, loss of appetite, generally feeling unwell, itching, light-coloured urine
- Irregular heart beat
- Liver dysfunction.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**5** HOW TO STORE OCTREOTIDE

Keep out of the reach and sight of children.

Do not use Octreotide after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Storage conditions:
**Before opening:** Store in a refrigerator 2-8°C, protected from light. Do not freeze.

**After opening:** The product must be used immediately and any unused drug-product must be discarded.

**After dilution:** The chemical and physical stability of Octreotide solution diluted in 9 mg/ml (0.9%) sodium chloride solution for infusion has been demonstrated for 24 hours when stored below 25°C. From a microbiological point of view, the product should be used immediately, if not used immediately, storage times and conditions are the responsibility of the user, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use unless the solution is clear and free from visible particles.

For single use only.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

**6** FURTHER INFORMATION

What Octreotide contains
- The active substance is octreotide (as the acetate).
  Each ml of solution for injection or concentrate for solution for infusion contains 0.05 mg, 0.1 mg and
The following side effects have also been reported and the approximate frequencies shown:

**Very common:**
- Stomach ache, nausea, wind, diarrhoea or constipation. (These will be less if you inject between meals or before going to bed)
- Changes in blood sugar levels (hyperglycaemia)
- Headache
- Gallstones
- Local pain at the site of injection.

**Common:**
- Slow heart beat
- Hair loss
- Itching
- Rash
- Shortness of breath
- Dizziness
- Loss of appetite
- Changes in blood sugar levels (hypoglycaemia)
- Impaired glucose tolerance
- Stomach discomfort after a meal
- Vomiting
- Bloating of stomach
- Loose faeces (stools)
- Discolouration of faeces
- Fat in your faeces (pale and fatty loose stools)
- Inflammation of the gallbladder
- Biliary sludge
- Yellow skin and eyes
- Abnormal liver function test results
- Changes in activity of the thyroid gland (hypothyroidism) causing changes in heart rate, appetite or weight, tiredness, feeling cold or sweating too much, anxiety or swelling at the front of the neck.

**0.5 mg octreotide.**
- The other ingredients are glacial acetic acid, sodium acetate trihydrate (E262), mannitol (E421) and water for injections.

**What Octreotide looks like and contents of the pack**
Octreotide 0.05 mg/ml, 0.1 mg/ml and 0.5 mg/ml solution for injection or concentrate for solution for infusion is a clear and colourless solution. The solution is supplied in colourless glass vials closed with serum rubber stoppers and sealed with aluminium flip-off caps fitted with plastic flip-off discs. The product is packed in cardboard boxes.

Octreotide 0.05 mg/ml, 0.1 mg/ml and 0.5 mg/ml solution for injection or concentrate for solution for infusion is available in pack sizes of 1, 3, 5, 6, 10, 20 and 30 vials.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

**Marketing Authorisation Holder**
Teva UK Limited, Eastbourne, BN22 9AG, United Kingdom

**Manufacturer**
Teva Pharmaceutical Works Private Limited Company H-2100 Gödöllő Táncsics Mihály út 82 Hungary

This leaflet was last revised in November 2011

PL 00289/1257
PL 00289/1264-5

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**After dilution:** The chemical and physical stability of Octreotide solution diluted in 9 mg/ml (0.9%) sodium chloride solution for infusion has been demonstrated for 24 hours when stored below 25°C. From a microbiological point of view, the product should be used immediately, if not used immediately, storage times and conditions are the responsibility of the user, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use unless the solution is clear and free from visible particles.

**Disposal:** Any unused product or waste material should be disposed of in accordance with local requirements.
The text version of the PIL has been provided for Octreotide 0.2mg/mL Solution for Injection or Concentrate for Solution for Infusion and approved as part of this application. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the leaflet mock-up has been obtained.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Octreotide 0.2 mg/ml Solution for injection or Concentrate for solution for infusion

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Octreotide is and what it is used for
2. Before Octreotide is used
3. How to use Octreotide
4. Possible side effects
5. How to store Octreotide
6. Further information

1. WHAT OCTREOTIDE IS AND WHAT IT IS USED FOR

Octreotide is a synthetic form of a hormone called somatostatin which occurs naturally in the body. It helps stop the release of some hormones, including growth hormone, in the body.

Octreotide is used:

- To treat acromegaly
  Acromegaly is a condition where the body produces too much growth hormone. The level of growth hormone controls the growth of tissues, organs and bones. Too much hormone means the size of bones and tissues, especially in the hands and feet, is larger than normal. The symptoms of acromegaly include headache, excessive perspiration, numb hands and feet, tiredness and joint pain. In most cases, the overproduction of growth hormone is caused by an enlargement in the pituitary gland (a pituitary adenoma).

Octreotide is used to treat people with acromegaly:
- when other types of treatment for acromegaly (surgery or radiotherapy) are not suitable or have not worked;
- after radiotherapy, to cover the interim period until the radiotherapy becomes fully effective;
- before surgery on the pituitary gland

- To relieve stomach or bowel symptoms associated with certain tumours known as 'gastroenteropancreatic' tumours (rare tumours of the stomach, bowels or pancreas)
  Overproduction of specific hormones and other related natural substances can be caused by some rare conditions of the stomach, bowels or pancreas. This upsets the natural hormonal balance of the body, and results in a variety of symptoms, such as flushing, diarrhoea, low blood pressure, rash and weight loss. Treatment with Octreotide helps to control these symptoms.

- To prevent complications following pancreatic surgery
Octreotide can be used in some patients when they have an operation on the pancreas. It may help reduce some of the problems which can occur in the abdomen after the operation, such as inflammation (swelling) and infection.

2. **BEFORE OCTREOTIDE IS USED**

**You should NOT be given Octreotide**
- if you are allergic (hypersensitive) to octreotide acetate or any of the other ingredients of Octreotide (see section 6)
- if you are breast-feeding.

**Take special care with Octreotide**
- if you are pregnant
- as octreotide may affect your blood sugar levels. You or your doctor should closely monitor you blood sugar levels.
- if you have any thyroid problems, or have had a disease which may have affected your thyroid.
- if you have any problems with your liver, or have you had a disease which may have affected your liver
- if you have ever suffered from gallstones or other stomach problems
- if you have a history of Vitamin B\textsubscript{12} deficiency. Your doctor may need to monitor your vitamin B\textsubscript{12} levels during therapy with octreotide.

Your doctor may want to give you a check up from time to time while you are being treated with Octreotide.

Growth hormone secreting pituitary tumours may sometimes expand and cause problems. Tell your doctor if you experience any problems with your eyes or sight.

Tell your doctor if your stomach or bowel problems get worse.

**Taking other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any of the following medicines, including medicines obtained without a prescription.

- Insulin or other drugs for diabetes
- Ciclosporin (a drug used after a transplant)
- Cimetidine (a drug used to reduce stomach acid)
- Bromocriptine (a drug used in Parkinson’s disease or in acromegaly or to suppress breast milk)
- Medicines to control blood pressure (beta-blockers or calcium channel blockers) or agents to control fluid and electrolyte balance (diuretics)
- Medicines metabolised by the liver for example carbamazepine (a drug used in psychiatric disorders, epilepsy, trigeminal neuralgia and neuropathy), digoxin (medicine for certain heart problems) and warfarin (a drug used to thin the blood) and terfenadine (to relieve allergic symptoms).

Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicines. You should not use Octreotide if you are pregnant unless you have been told by your doctor that it is absolutely necessary for you to do so.
You should not breast-feed your infant whilst receiving treatment with octreotide, unless you have been told to do so.

**Driving and using machines**
Octreotide may make you feel dizzy. If this happens, do not drive or operate machinery. Remember that if you are unwell your ability to operate machinery may be affected.

**Important information about some of the ingredients of Octreotide**
Octreotide 0.2 mg/ml solution for injection or concentrate for solution for infusion contains less than 1 mmol sodium per dose, i.e. essentially “sodium-free”.

Other Special Warnings

- Tell your doctor if your stomach or bowel symptoms get worse
- Octreotide should only be used in pregnancy if clearly needed. Tell your doctor if you are pregnant or want to become pregnant
- Women of child bearing potential must use an effective contraceptive method during treatment with Octreotide

3. **HOW TO USE OCTREOTIDE**

Always use Octreotide exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure of anything.

Your medicine must be injected subcutaneously i.e. into the tissue under the skin. Your doctor or nurse will show you how to do this. If you are unsure, go back and ask for advice. You must use a clean, sterile syringe and needle every time.

The upper arms, thighs and stomach are good areas for subcutaneous injection. Choose a different place each time so that you don’t irritate a particular area. Keep changing the injection site. Don’t inject into the same place too frequently.

To avoid side effects like stomach ache, wind, diarrhoea and constipation do not inject at mealtimes. Inject between meals or before going to bed.

In rare cases Octreotide will have to be injected intravenously (into a vein). If this is necessary the doctor or nurse will do it and monitor you closely. You must NOT inject Octreotide into your veins yourself.

The usual dosages are given below; however your doctor will decide what dosage to give to you, as this depends on the nature of your treatment, your age and your medical condition:

**For the treatment of acromegaly**

- The usual dose is 0.1 to 0.2 mg three times a day by subcutaneous injection. Depending on how you respond, your doctor will adjust the dose until they find the right dose.

**To relieve symptoms caused by over-production of some hormones**

- Your doctor will usually start your treatment with 0.05 mg once or twice daily by subcutaneous injection. Depending on how you respond, your doctor may gradually increase the dose until they find your ideal dose.
To prevent complications following pancreatic surgery

- 0.1 mg three times a day for seven days starting on the day of the operation.

People with liver or kidney problems may be given a smaller dose.

There is very little experience of using octreotide in children

If you receive more Octreotide than you should

If you are concerned that you may have been given too much Octreotide, tell your doctor or nurse immediately.

If you miss a dose of Octreotide

As you will be given this medicine under close supervision, it is very unlikely that you will miss a dose. If you think that you have missed a dose of treatment, tell a doctor or nurse at once.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Octreotide can cause side effects, although not everybody gets them.

Most people who are prescribed Octreotide benefit from taking it, but a few people can be upset by it. If you are receiving this medicine on a long term basis then you will go to hospital from time to time to have regular check-ups.

There is no need to worry if you suffer from any of the following common reactions at the site of injection:

- Pain, stinging, tingling, burning, redness and swelling.
These rarely last for more than 15 minutes and will be less if you let your medicine reach room temperature before injecting.

Some side effects can be serious. Stop taking Octreotide and tell your doctor straight away if you notice that:

- Your face becomes flushed or swollen or you develop spots or a rash
- Your chest feels tight, you become short of breath or wheezy
- You feel faint, possibly as a result of a fall in blood pressure.
These might be a result of an allergic reaction.

If you develop any of the following see your doctor immediately:

- Prolonged/troublesome bloating of the stomach with pain
- Nausea/vomiting associated with drowsiness
- Feeling restless or giddy
- Yellowing of the skin or whites of your eyes
- Acute pancreatitis (sudden, severe, burning pains in the stomach). This may happen within the first few hours or days of treatment and resolves itself upon drug withdrawal.

The following side effects have also been reported and the approximate frequencies shown:

Very common (≥1/10)
PAR-Octreotide 0.05mg/ml, 0.1mg/ml, 0.2mg/ml & 0.5mg/ml Solution for Injection or Concentrate for Solution for Infusion

UK/H/2339/01-03/DC & UK/H/2340/01/DC

Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

**Very common:**
- Stomach ache, nausea, wind, diarrhoea or constipation. (These will be less if you inject between meals or before going to bed).
- Changes in blood sugar levels (hyperglycaemia)
- Headache
- Gallstones
- Local pain at the site of injection

**Common:**
- Slow heart beat
- Hair loss
- Itching
- Rash
- Shortness of breath
- Dizziness
- Loss of appetite
- Changes in blood sugar levels (hypoglycaemia)
- Impaired glucose tolerance
- Stomach discomfort after a meal
- Vomiting
- Bloating
- Loose faeces (stools)
- Discolouration of faeces
- Fat in your faeces (pale and fatty loose stools)
- Inflammation of the gallbladder
- Biliary sludge
- Yellow skin and eyes
- Abnormal liver function test results
- Changes in activity of the thyroid gland (hypothyroidism) causing changes in heart rate, appetite or weight, tiredness, feeling cold or sweating too much, anxiety or swelling at the front of the neck.

**Uncommon:**
- Dehydration
- Fast heart beat

**Frequency not known:**
- Anaphylaxis (a type of allergic reaction which causes difficulty in breathing or dizziness), allergy/hypersensitivity reactions
- Itchy rash
- Inflammation of the pancreas
- Liver inflammation (hepatitis); symptoms may include yellowing of the skin and eyes (jaundice), nausea, vomiting, loss of appetite, generally feeling unwell, itching, light-coloured urine
- Irregular heart beat
Liver dysfunction.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE OCTREOTIDE

Keep out of the reach and sight of children.

Do not use Octreotide after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Storage conditions:
Before opening: Store in a refrigerator 2-8°C, protected from light. Do not freeze.

After opening: Opened vials may be stored for 2 weeks at room temperature for day to day use.

After dilution: The chemical and physical stability of Octreotide solution diluted in 9 mg/ml (0.9%) sodium chloride solution for infusion has been demonstrated for 24 hours when stored below 25°C. From a microbiological point of view, the product should be used immediately, if not used immediately, storage times and conditions are the responsibility of the user, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use unless the solution is clear and free from visible particles.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Octreotide contains

- The active substance is octreotide (as the acetate).
  Each ml of solution for injection or concentrate for solution for infusion contains 0.2 mg octreotide.

- The other ingredients are glacial acetic acid, sodium acetate trihydrate (E262), mannitol (E421), phenol and water for injections.

What Octreotide looks like and contents of the pack

Octreotide 0.2 mg/ml solution for injection or concentrate for solution for infusion is a clear and colourless solution. The solution is supplied in colourless glass vials closed with serum rubber stoppers and sealed with aluminium flip-off caps fitted with plastic flip-off discs. The product is packed in cardboard boxes.

Octreotide 0.2 mg/ml solution for injection or concentrate for solution for infusion is available in pack sizes of 1, 5, and 10 vials.

Not all pack sizes may be marketed.
Marketing Authorisation Holder
Teva UK Limited, Eastbourne, BN22 9AG, United Kingdom

Manufacturer
Teva Pharmaceutical Works Private Limited Company
H-2100 Gödöllő
Táncsics Mihály út 82
Hungary

This leaflet was last revised in November 2011.

PL 00289/1140

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The following information is intended for medical or healthcare professionals only:

Instructions for use, handling and disposal:

Octreotide Teva is an injection and a concentrate for solution for infusion. This must be handled with caution. The dilution must be done under aseptic conditions, by trained staff and in a specific area. The contact of Octreotide Teva with skin and membranes should be avoided. If the solution comes into contact with the skin: wash with water and soap. If the solution comes into contact with membranes, wash (irrigate) the affected area with water.

To reduce local discomfort, let the solution reach room temperature before injecting. Avoid multiple injections at short intervals at the same time.

To prevent contamination, it is recommended to puncture the cap of the vial not more than 10 times.

Storage:

Storage conditions:
Before opening: Store in a refrigerator 2-8°C, protected from light. Do not freeze.

After opening: Opened vials may be stored for 2 weeks at room temperature for day to day use.

After dilution: The chemical and physical stability of Octreotide Teva solution diluted in 9 mg/ml (0.9%) sodium chloride solution for infusion has been demonstrated for 24 hours when stored below 25°C. From a microbiological point of view, the product should be used immediately, if not used immediately, storage times and conditions are the responsibility of the user, unless dilution has taken place in controlled and validated aseptic conditions.

Do not use unless the solution is clear and free from visible particles.

Disposal:

Any unused product or waste material should be disposed of in accordance with local requirements.
PAR-Octreotide 0.05mg/ml, 0.1mg/ml, 0.2mg/ml & 0.5mg/ml Solution for Injection or Concentrate for Solution for Infusion

UK/H/2339/01-03/DC & UK/H/2340/01/DC

Octreotide 0.5 mg/ml
Solution for Injection or Concentrate for Solution for Infusion

0.5 mg
1 ml

CONCENTRATION
Check all solutions for dilution or concentrate for solution for infusion contain 0.5 mg of octreotide (as octreotide acetate).

EXCIPIENTS
Sodium chloride added, sodium hydroxide or hydrochloric acid used to adjust neutral. 0.15%, 0.9% or 5% w/v sodium chloride added for further dilution.

For further dilution, refer to package insert for further information.

Octreotide 0.5 mg/ml
Solution for Injection or Concentrate for Solution for Infusion

SPECIAL WARNING
For single use only. Please read the package leaflet before use.

Do not use the drug as a substitute for medical treatment given by the doctor.

Keep out of the reach of children and pets.

Octreotide 0.5 mg/ml
Solution for Injection (s.c.) or Concentrate for Solution for Infusion

1 ml vial
Solution for injection (s.c.) or concentrate for solution for infusion

Teva UK Ltd. PL 00269/1265

1-29133260/A 61298-A

- 20 -
Carton
The text version of the label for Octreotide 0.2 mg/mL Solution for Injection or Concentrate for Solution for Infusion has been provided and approved as part of this application. In accordance with medicines legislation, this product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

Octreotide 0.2 mg/ml solution for injection or concentrate for solution for infusion octreotide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml of solution for injection or concentrate for solution for infusion contains 0.2 mg of octreotide (as octreotide acetate).

3. LIST OF EXCIPIENTS

Glacial acetic acid, sodium acetate trihydrate (E262), mannitol (E421), phenol, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection (s.c.) or concentrate for solution for infusion.
1 vial (5 ml)
5 vials (5 ml)
10 vials (5 ml)

5. METHOD AND ROUTES OF ADMINISTRATION

Subcutaneous or intravenous use.
Read the package leaflet before use.
6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF REACH AND SIGHT OF CHILDREN

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator between 2-8°C, protected from light. Do not freeze.
After opening: Opened vials may be stored for 2 weeks at room temperature for day to day use.
For storage conditions of the diluted medicinal product see package leaflet.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva UK Ltd, Eastbourne, BN22 9AG

12. MARKETING AUTHORISATION NUMBERS

PL 00289/1140
13. **BATCH NUMBER**

Batch No:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

POM

15. **INSTRUCTIONS ON USE**

Use as directed by the doctor

16. **INFORMATION IN BRAILLE**

Justification for not including Braille accepted
### Label

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**VIAL LABEL**

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<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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<th>2. METHOD OF ADMINISTRATION</th>
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<td>Teva UK Ltd</td>
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<td>PL 00289/1140</td>
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Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the MHRA granted TEVA
UK Limited Marketing Authorisations for the medicinal products Octreotide 0.05 mg/mL, 0.1
mg/mL, 0.5 mg/mL and 0.2 mg/mL Solution for Injection or Concentrate for Solution for
Infusion (PL 00289/1257, PL 00289/1264-5; UK/H/2339/01-03/DC and PL 00289/1140;
UK/H/2340/01/DC) on the 23 December 2011

These are abridged applications for Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.5 mg/mL and 0.2
mg/mL Solution for Injection or Concentrate for Solution for Infusion, submitted under
Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic versions of the
reference products Sandostatin Ampoules Solution for Injection, 50 mcg/ml (PL
00101/0212), 100 mcg/ml (PL 00101/0213), and 500 mcg/ml (PL 00101/0214) authorised in
the UK to Novartis Pharmaceuticals UK Ltd in 1989 and Sandostatin Multidose Vial
1 mg/5 ml (PL 00101/0300) in 1990. The reference products have been authorised for a
period in excess of 10 years, thus the period of data exclusivity has expired.

Octreotide is a synthetic octapeptide analogue of somatostatin with similar properties but a
longer duration of action. It inhibits pathologically increased secretion of growth hormone
and of peptides and serotonin produced within the gastroenteropancreatic endocrine (GEP)
system. It is used as the acetate in the symptomatic management of neuroendocrine tumours
such as carcinoid tumours, VIPomas, and glucagonomas. Octreotide acetate is also used in
the treatment of acromegaly and the prevention of complications after pancreatic surgery.

No new non-clinical or clinical efficacy studies were conducted for this application, which is
acceptable given that the applications were for generic versions of products that have been
licensed for over 10 years. A bioequivalence study is not necessary to support these
applications for parenteral products.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP)
are in place for these product types at all sites responsible for the manufacture and assembly
of these products. Evidence of compliance with GMP has been provided for the named
manufacturing and assembly sites. For manufacturing sites within the Community, the RMS
has accepted copies of current manufacturer authorisations issued by inspection services of
the competent authorities as certification that acceptable standards of GMP are in place at
those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current
GMP certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange
of information’ issued by the inspection services of the competent authorities (or those
countries with which the EEA has a Mutual Recognition Agreement for their own territories)
as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system, as described by the MAH, fulfils the
requirements and provides adequate evidence that the MAH has the services of a qualified
person responsible for pharmacovigilance and has the necessary means for the notification of
any adverse reaction suspected of occurring either in the Community or in a third country.

The Marketing Authorisation Holder has provided adequate justification for not submitting a
Risk Management Plan (RMP). As the application is for a generic version of an already
authorised reference product, for which safety concerns requiring additional risk
minimisation have not been identified, a risk minimisation system is not considered
necessary. The reference products have been in use for many years and the safety profile of the active substance is well established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market.
II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Octreotide 0.05, 0.1, 0.2, 0.5 mg/ml Solution for Injection or Concentrate for Solution for Infusion.</th>
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<td>Octreotide Acetate</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antigrowth Hormones H01CB02</td>
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<td>Reference numbers for the Mutual Recognition Procedure</td>
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<td>Member States concerned</td>
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<td>Octreotide 0.2 mg/mL Solution for Injection or Concentrate for Solution for Infusion PL 00289/1140; UK/H/2340/01/DC: Germany and the Netherlands</td>
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<tr>
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<td>Octreotide 0.2 mg/mL Solution for Injection or Concentrate for Solution for Infusion</td>
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| Name and address of the authorisation holder | TEVA UK Limited  
Brampton Road,  
Hampden Park,  
Eastbourne,  
East Sussex BN22 9AG  
UNITED KINGDOM |
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

rINN name: Octreotide Acetate

Chemical name:
L-Cysteinamide, D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-Lysyl-L-threonyl-N-[(1R,2R)-2-hydroxy-1-(hydroxymethyl)propyl]-cyclic(2→7)-disulfide, acetate salt.

Molecular formula: C_{49}H_{66}N_{10}O_{10}S_{2}
Molecular weight: 1019.3

Structure

D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol • acetate salt

General properties

Octreotide acetate is a long-acting, synthetic octapeptide with pharmacological properties mimicking those of the natural hormone, somatostatin. It is described as a white to off white powder that is soluble in water. The drug substance is hygroscopic, absorbing 3-5% water when exposed to atmospheric moisture and is stated to be stable when stored at 2-8°C, protected from light and air.

The active substance, octreotide acetate, is not currently the subject of a European Pharmacopoeia (Ph.Eur.) monograph. The active substance is controlled by an in-house specification which is satisfactory.

Manufacture

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate data have been supplied to characterise the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidance concerning contact with foodstuffs.

Appropriate stability data have been generated to support a suitable re-test period when stored in the proposed packaging.
DRUG PRODUCT
Description and Composition
The drug products are presented as clear colourless solutions. Each mL of solution for injection or concentrate for solution for infusion contains 0.05 mg, 0.1 mg, 0.2 mg and 0.5 mg of octreotide (as octreotide acetate) respectively for the different strengths of the product.

Other ingredients consist of pharmaceutical excipients, glacial acetic acid (pH adjustment), sodium acetate trihydrate (for pH adjustment) (E262), mannitol (E421), water for injections and phenol (for 0.2 mg/mL strength only).

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Appropriate justification for the inclusion of each excipient has been provided. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for the proposed product. Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

Pharmaceutical development
Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop robust, stable, generic formulations, bioequivalent to the innovator products, Sandostatin® Ampoules 50 mcg/mL, 100 mcg/mL, 500 mcg/mL solution for injection or concentrate for solution for infusion and Sandostatin Multidose Vial 1 mg/5 ml (PL 00101/0300) (Novartis Pharmaceuticals UK Limited). Suitable pharmaceutical development data have been provided for these applications.

The physico-chemical properties of the drug products have been compared with the reference products. These data demonstrate that the proposed products can be considered generic medicinal products of Sandostatin® Ampoules 50 mcg/mL, 100 mcg/mL, 500 mcg/mL solution for injection or concentrate for solution for infusion and Sandostatin Multidose Vial 1 mg/5 ml (PL 00101/0300) (Novartis Pharmaceuticals UK Limited).

Impurity profiles
Comparative impurity data were provided for the proposed and reference products. The impurity profiles were found to be similar, with all impurities within specification limits.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies have been conducted on all four dosage strengths at the lower batch-scale defined for commercial use and are satisfactory. The validation data demonstrate consistency of the manufacturing process.

Finished Product Specification
Finished product specifications are provided for both release and shelf-life, and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.
Container-Closure System
The finished product is licensed for marketing in clear glass vials closed with rubber stoppers and sealed with aluminium flip-off caps fitted with plastic flip-off discs. The product are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons and are packaged in pack sizes of 1, 3, 5, 6, 10, 20 and 30 vials (1, 5, 10 vials for 0.2 mg/mL strength). The Marketing Authorisation Holder has committed to submitting the proposed packaging/labelling for any pack size for approval before it is marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended).

Stability
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months (unopened) for the 0.05 mg/ml, 0.1 mg/ml and 0.5 mg/ml strengths and 24 months (unopened) for the 0.2 mg/ml formulation, and 2 weeks at room temperature for day to day use (for 0.2 mg/mL strength only) has been approved. Storage conditions for unopened vials are Store in a refrigerator (2-8°C) protected from light. Do not freeze”. For storage conditions of the medicinal product after dilution please check Section 6.3 of the SmPC.

Bioequivalence Studies
The product is formulated for administration as a solution by intravenous or subcutaneous route.

The proposed and reference products have the same qualitative and quantitative composition in terms of active substance. The excipients of the reference and proposed products differ; however, the applicant has provided the results of viscosity tests which demonstrate that the proposed products are similar to the reference. Therefore, a bioequivalence study is not needed for these applications

An evaluation of the justification for the non-submission of a bioequivalence study can be found in the ‘Clinical Aspects’ section of this report.

Quality Overall Summary
A satisfactory quality overall summary is provided and has been prepared by an appropriately qualified expert. The curriculum vitae of the expert has been provided.

Summary of Product Characteristic (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically acceptable. Colour mock-ups of some of the labelling and PIL have been provided. These are satisfactory. Where text versions of the label and PIL have been submitted, these have been approved and the applicant has provided a commitment not to market these products until full colour mock-ups have been approved by the relevant regulatory authority.

The applicant has submitted results of PIL user testing of the 0.05, 0.1 and the 0.5 mg/ml strengths. A bridging report has been provided for the 0.2 mg/ml strength. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the leaflet contains.

MAA Form
The MAA form is pharmaceutically satisfactory.
Conclusion
There are no objections to the approval of Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
The pharmacodynamic, pharmacokinetic and toxicological properties of octreotide acetate are well-known. Therefore, no further studies are required and the applicant has not provided any.

ENVIRONMENTAL RISK ASSESSMENT
No formal Environmental Risk Assessment has been provided. The applicant has justified its absence adequately. As a generic product, the use of this product is not expected to increase the overall use of octreotide acetate and so no additional increase in environmental risk has been identified.

NON-CLINICAL OVERVIEW
The non-clinical overview was written by a suitably qualified expert and is satisfactory. The curriculum vitae of the expert has been provided.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPCs)
The SmPCs are satisfactory from a non-clinical viewpoint and are consistent with those for the reference products.

There are no objections to the approval of Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion from a non-clinical point of view.

III.3 CLINICAL ASPECTS

INDICATIONS

GEP tumours:

For the relief of symptoms associated with functional gastroenteropancreatic endocrine tumours including:

- Carcinoid tumours with features of carcinoid syndrome
- VIPomas
- Glucagonomas

Octreotide is not an antitumour therapy and is not curative in these patients.

Acromegaly:

For symptomatic control and reduction of growth hormone and somatomedin c plasma levels in patients with acromegaly:

- In short term treatment, prior to pituitary surgery, or
- In long term treatment in those who are inadequately controlled by pituitary surgery, radiotherapy, or in the interim period until radiotherapy becomes effective.

Octreotide is indicated for acromegalic patients for whom surgery is inappropriate.
Evidence from short term studies demonstrate that tumour size is reduced in some patients (prior to surgery) further tumour shrinkage however cannot be expected as a feature of continued long term treatment.

Prevention of complications following pancreatic surgery.

The indications are consistent with those for the reference products and are satisfactory.

**POSOLOGY AND METHOD OF ADMINISTRATION**

Octreotide Solution for Injection or Concentrate for Solution for Infusion is to be used either subcutaneously or via the intravenous route.

The posology and method of administration for the proposed products are in line with those for the reference medicinal products.

**TOXICOLOGY**

The toxicology of octreotide acetate is well-known. No new data have been submitted and none are required for these types of applications.

**CLINICAL PHARMACOLOGY**

The clinical pharmacology of octreotide acetate is well-known. No novel pharmacodynamic or pharmacokinetic data are supplied or required for this application.

*Pharmacokinetics*

No new data have been submitted and none are required for applications of this type.

Octreotide Solution 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion are generic versions of Sandostatin Ampoules Solution for Injection, 50 mcg/ml (PL 00101/0212), 100 mcg/ml (PL 00101/0213), 500 mcg/ml (PL 00101/0214) and Sandostatin Multidose Vial 1 mg/5 ml (PL 00101/0300) authorised to Novartis Pharmaceuticals UK Ltd. The use of these reference products is established in the UK. Both the reference and proposed products contain the same quantitative and qualitative composition of the active ingredient, octreotide acetate.

According to CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, Parenteral solutions).

In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are not required. Moreover, a bioequivalence study is not required for an aqueous parenteral solution with comparable excipients in similar amounts, if it can be demonstrated that the excipients have no impact on viscosity.

The proposed and reference products contain the same quantitative composition of the active ingredient, octreotide acetate. The list of excipients, however, differs between the proposed and reference products. The applicant has provided the results of viscosity tests which demonstrate that the viscosity of the proposed products is similar to that of the reference products. Therefore, a bioequivalence study is not needed for these applications.

*Pharmacodynamics*

No new data have been submitted and none are required for an application of this type.
Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
No new safety data have been submitted or are required for these generic applications. As octreotide acetate is a well-known substance with an acceptable adverse event profile, this is satisfactory.

Expert Report
A satisfactory clinical overview is provided, which has been prepared by an appropriately qualified physician. The curriculum vitae of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in line with current requirements.

MAA form
The MAA form is medically satisfactory.

Conclusion
There are no objections to the approval of Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
The applicant’s Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion products have been demonstrated to be generic versions of the reference products Sandostatin Ampoules Solution for Injection, 50 mcg/ml (PL 00101/0212), 100 mcg/ml (PL 00101/0213), and 500 mcg/ml (PL 00101/0214) and to Sandostatin Multidose Vial 1 mg/5 ml (PL 00101/0300) (Novartis Pharmaceuticals UK Limited).

No new or unexpected safety concerns arose from these applications.

PRODUCT LITERATURE
The SmPC and PIL are acceptable, and consistent with those for the reference products. The labelling is acceptable and in line with current requirements.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Octreotide 0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL and 0.5 mg/mL Solution for Injection or Concentrate for Solution for Infusion and the reference products Sandostatin Ampoules Solution for Injection, 50 mcg/ml (PL 00101/0212), 100 mcg/ml (PL 00101/0213), and 500 mcg/ml (PL 00101/0214) and Sandostatin Multidose Vial 1 mg/5 ml (PL 00101/0300) (Novartis Pharmaceuticals UK Limited), are interchangeable. Extensive clinical experience with octreotide acetate is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk balance is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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